PANEL DISCUSSION: MORNING SESSION*

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DR. NEU: Dr. Washington, would you care to express an opinion about MIC values compared to susceptible and resistant?

DR. WASHINGTON: I think that MICs are not necessary for ordinary clinical care. There is nothing wrong with the Bauer-Kirby disc method. The results are as accurate and reproducible as those one can obtain with dilution methods. There are, however, increasing numbers of dilution kits that contain lyophilized or frozen antibiotics. They are becoming very convenient for laboratories. I think such MIC methods are often introduced without proper information, indoctrination, or education on interpreting the results. But, basically, I do not think that there are many instances where MIC's are indicated, and I think their potential for misinterpretations can be very serious.

DR. NEU: Dr. Gilbert, do you use MICs at your institution?

DR. GILBERT: No, we are still using the Bauer-Kirby disc method. However, we have become increasingly concerned about the cell-bound cephalosporinase issue, for example, with *Enterobacter, Serratia,* and *Pseudomonas aeruginosa* infections. If the situation is one in which we need long term antibiotics and the results depend on good antimicrobic activities, for example, septic arthritis, we will perform macrotube dilution for MICs and MBCs with high inocula which we cannot do with the standard laboratory test procedure.

DR. NEU: Dr. Parry, you are in a large community hospital. Are you using MICs?

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DR. PARRY: We are using MICs, but I must say that for me the majority of isolates and in most clinical situations MICs are not more useful than the Bauer-Kirby disc method. I think MICs are most useful in instructing physicians that aminoglycosides are not as good as they thought they were, and that the aminoglycoside MICs are relatively high. The physician sees the narrow toxic to therapeutic ratio, which he did not appreciate before. The MIC of the *Pseudomonas* is 2 ug/ml, and the blood level is only 4 ug/ml. So MICs have been useful in an occasional clinical situation. MICs have been useful in instructing physicians how they should use drugs such as the aminoglycosides.

DR. NEU: I think MICs have been useful in our own situation and that the physicians have altered their prescibing habits to a certain degree when they realize what you have just mentioned. Physicians are more likely to use an appropriate drug.

DR. GILBERT: I am a little bit confused whether an inhibitory quotient (IQ) of 100 makes any difference as compared to an inhibitory quotient of 10? If we have an *E. coli* susceptible to ampicillin and we can achieve serum concentrations that are eight, nine, or 10 times above the MIC, is that worse than the high IQ found for cefotaxime or moxalactam? Does the high IQ make any difference in the outcome for the patient?

DR. NEU: A very high IQ probably doesn't make any difference. But the high IQ does indicate that one could give the drug twice a day if one has a very low MIC, one reduces the number of organisms to such a low level that it is not necessary to give another dose for about eight, 10, or 12 hours.

DR. WASHINGTON: Depression of growth can result in false susceptibilities. Many laboratories use some of the rapid methodologies where results are obtainable in a period of three or four hours. There are certain organisms, for example, *Enterobacter* and the methicillin-resistant staphylococci, where the initial killing is great, and the regrowth is beyond the input of the instrument. In other words, it occurs beyond four hours, so it is never picked up.

DR. NEU: I said at the end of my lecture that for an organism susceptible to ampicillin, I would use ampicillin as the drug rather than one of the new ones I chose initially. I think that if patients enter the hospital from the community, never seeing antibiotics, that it is reasonable to use ampicillin or cefazolin as initial therapy. If they developed infection in the hospital or have been in a multistage operation, the physician often starts with three drugs, and then it seems to me that it would be wiser to

use one of the new agents for the first 24 hours until the laboratory studies show exactly what is the infecting agent. Our big problem is tryng to modify behavior after it has already set in. It seems that a cement occurs once the physician has started some drug. He does not want to change, particularly if the patient is better.

DR. PARRY: Dr. Gilbert, I would like you to comment on prophylaxis, particularly with respect to prosthetic hip replacement, where the physician, the orthopedic surgeon, objects to single dose prophylaxis based on the statement that "I am going to leave the Hemovac in for four or five days and I want to have a prophylactic agent on board to prevent staphylococci traveling down the tubes of the Hemovac for that period of time." How do you respond to that?

DR. GILBERT: No data. The cardiac surgeons say the same thing. "I'm putting in a new valve and I am going to have this arterial line in for two days," or "I'm going to have these chest tubes under the sternum for two days, etc., etc.", and I think until we have more information on those particulars, we do what we can do. I think that we have made great progress. We have gone from several weeks of prophylaxis to a few days, and now, in some circumstances, down to one dose. So I feel that it is a triumph if for the orthopedic surgical situation you describe we get away with two days.

DR. BEAM: In reference to the question regarding cardiac surgery prophylaxis, I would like to mention that we have three ongoing trials comparing third generation cephalosporins, cefazolin, and cephalothin. With cephalothin it is important to realize that a one gram dose is totally inadequate. The tissue concentrations in at least 40% of the cases do not reach the MIC values. If one gives a two gram dose, one can measure detectable tissue concentrations, but only for less than four hours. If surgery goes beyond three hours, the surgeons should administer another two grams of cephalothin. Cefazolin, in contrast, with a one gram prophylaxis dose usually gives concentrations above both MIC and MBC for the duration of the surgical procedure and these tissue concentrations are in parasternal musculature, sternum per se, and atrial appendage.

QUESTION FROM THE AUDIENCE: Please comment on the use of MIC in the problem of tolerance.

DR. WASHINGTON: Tolerance has become a very popular subject. As an editor of a journal on antimicrobial agents, I see a lot more papers on tolerance than I care to. I always preface any remarks about tolerance by reminding you that it was originally described for the pneumococcus and

penicillin. To the best of my knowledge, pneumococci have not been a particular therapeutic problem with penicillin. The attention is mostly with staphylococcus. The difficulty is that the demonstration of tolerance is so completely methodologically determined that one can almost decide in advance whether or not one wants to demonstrate tolerance. Some tolerance is an artifact. It is very much related to what steps one takes to try to avoid having organisms above the meniscus in the test tube that are not fully exposed to the antimicrobial agent in question and, therefore, survive the exposure and can be subcultured at a later time. We have a large number of patients with *Staph. aureus* bacteremia who have had MBCs performed and have tolerance demonstrated, but we have not been able to determine any difference in their outcome related to tolerance. The other interesting thing is that if one follows these patients with a serum bactericidal test, for whatever that is worth, one will never demonstrate tolerance in the bactercidal test. In other words, the phenomenon is eliminated in the presence of serum. To the best of my knowledge, no clear-cut clinical data or even experimental animal data substantiate the importance of tolerance except for the enterococcus.

QUESTION FROM THE AUDIENCE: Regarding the hypoprothrombinemia with specific drugs that have the methylthiotetrazole side chain, will vitamin K override the hypoprothrombinemia effect?

DR. PARRY: Yes.

SAME QUESTIONER: Theoretically, hypoprothrombinemia should not be a major risk if one has an intact liver and can respond to Vitamin K. Would you ever consider giving prophylactic vitamin K?

DR. PARRY: If one is aware of the problem and gives Vitamin K, the situation can be corrected, but it does not always occur immediately. Hypoprothrombinemia occurs primarily when the patient is receiving a vitamin K deficient diet. Either they are postoperative and not eating or they are on total parenteral nutrition without Vitamin K. That is where the hypoprothrombinemia is observed.

DR. NEU: Are there any other questions or comments?

QUESTION FROM THE AUDIENCE: How can one monitor sufficient tissue levels to make sure of getting at the bug that one is trying to get at?

DR. NEU: I think that it is almost impossible to measure tissue concentrations. Most of these new drugs with very good pharmacokinetic properties enter into most of the compartments in which one would expect to see an infection. So if the drugs are used every eight or 12 hours, adequate tissue concentrations will be achieved.

DR. GILBERT: In addition to the pharmacologic considerations, the bottom line is the clinical appearance of the patient. If the patient is getting better, one is probably achieving adequate tissue concentration. I mean one can do an *in vivo* sensitivity test. Draw blood cultures to see if they are sterile, reaspirate the joint, repeat the spinal tap.

QUESTION FROM THE AUDIENCE: Earlier in the discussion there were comments regarding the nutritional status of the patient and hypoprothrombinemia. Could you clarify the role of the side chain?

DR. PARRY: Yes, it appears that there is some *in vitro* work with microsomal enzymes, looking at the specific activity of that side chain on the synthesis of vitamin K. I tried to stress that older concepts about interference with gut flora and their synthesis of vitamin K would be expected more predictably with some of the other new compounds like ceftriaxone, a third generation compound with extremely high fecal levels. But this drug does not produce the hypoprothrombinemia that is seen with cefamandole, moxalactam, or cefoperazone. Hypoprothrombinemia has not been encountered with cefotaxime, which does not have that side chain. So, with the current information we have it would appear to be a specific effect of that side chain.

DR. NEU: Dr. Lipsky's group at Johns Hopkins has postulated that the methylthiotetrazole moiety forms a dimer that interferes with vitamin K synthesis. It may be that a compound such as moxalactam that has an oxygen atom in the nucleus is more reactive than when a sulphur is present. It is probable that within the gut part of the drug is broken down and the side chain falls off. One obviously could correct the defect with vitamin K, but if one has both a platelet and a prothrombin defect and a damaged mucosal surface, one must be aware of the risks of bleeding. The major thing is to realize that bleeding can occur.

DR. NEU: I should add a caution that some patients who received 10 mg of vitamin K once a week and received drugs with the methylthiotetrazole side chain have still had their prothrombin times altered. One may have to give vitamin K a number of times each week. Further, unlike the rapid correction of prothrombi values when prolonged by use of oral anticoagulants, the prothrombin time may not return to normal for 24 hours.